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Validation of an algorithm-based definition of treatment resistance in patients with schizophrenia

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ABSTRACT

Large-scale pharmacoepidemiological research on treatment resistance relies on accurate identification of people with treatment-resistant schizophrenia (TRS) based on data that are retrievable from administrative registers. This is usually approached by operationalising clinical treatment guidelines by using prescription and hospital admission information. We examined the accuracy of an algorithm-based definition of TRS based on clozapine prescription and/or meeting algorithm-based eligibility criteria for clozapine against a gold standard definition using case notes. We additionally validated a definition entirely based on clozapine prescription. 139 schizophrenia patients aged 18–65 years were followed for a mean of 5 years after first presentation to psychiatric services in South-London, UK. The diagnostic accuracy of the algorithm-based measure against the gold standard was measured with sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). A total of 45 (32.4%) schizophrenia patients met the criteria for the gold standard definition of TRS; applying the algorithm-based definition to the same cohort led to 44 (31.7%) patients fulfilling criteria for TRS with sensitivity, specificity, PPV and NPV of 62.2%, 83.0%, 63.6% and 82.1%, respectively. The definition based on lifetime clozapine prescription had sensitivity, specificity, PPV and NPV of 40.0%, 94.7%, 78.3% and 76.7%, respectively. Although a perfect definition of TRS cannot be derived from available prescription and hospital registers, these results indicate that researchers can confidently use registries to identify individuals with TRS for research and clinical practices.

1. Introduction

Treatment-resistant schizophrenia (TRS) is a major cause of disability and functional impairment worldwide (Kennedy et al., 2014). Approximately 30% of patients with schizophrenia will develop TRS at some point during their illness course (Elkis and Buckley, 2016; Kane et al., 1988) with all standard treatment guidelines recommending these patients be treated with clozapine (National Collaborating Centre for Mental Health, 2009; National Institute for Health and Clinical Excellence guideline, 2014). The gold standard definition of TRS is defined as insufficient response to at least two sequential, different antipsychotic medications of adequate doses taken over an adequate time period (National Institute for Health and Clinical Excellence guideline, 2014); though the definition of insufficient response is open to interpretation (Howes et al., 2016).

When using register-based data, response, or lack thereof, to antipsychotics often has to be inferred from data on service use or changes in prescriptions. This has led researchers to design proxy measures of TRS (Huber et al., 2008). Some of the authors (J.M., C.G., H.T.H. and T.W.), using register data on prescriptions and psychiatric admissions, developed a definition of insufficient response, which is based on the clinical guidelines and recommendations, using the data available in the Danish prescription and hospital registers. While this definition of TRS has already yielded a wealth of insights into treatment-resistant schizophrenia (Wimberley et al., 2016a; Wimberley et al., 2016b; Wimberley et al., 2017a; Wimberley et al., 2017b; Horsdal et al., 2017), its validity against the gold standard definition has not been established.

Therefore, we aimed to validate the algorithm-based definition of TRS (Wimberley et al., 2016b) compared to the gold standard definition

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of TRS using the longitudinal data from a well-characterised sample of patients with first-episode schizophrenia (FES) collected in South-London and who were assessed after first five years of illness (Ajnakina et al., 2017; Lally et al., 2016). Another more simple definition of TRS is based exclusively on lifetime clozapine prescription, and has been used in a number of studies (Manuel et al., 2012; Wheeler et al., 2014; Wimberley et al., 2016a, 2016b; Horsdal et al., 2017). We additionally validated this clozapine definition, which we expect would have close to 100% in positive predictive value for detecting TRS patients.

2. Methods

2.1. Sample

Participants were recruited as part of the National Institute of Health Research (NIHR) Biomedical Research Centre (BRC) Genetics and Psychosis (GAP) study conducted in South-London, UK between December 2005 and October 2010. Further details of the sample are available in Supplementary material and Di Forti et al., 2014. Among 283 first-episode schizophrenia spectrum psychosis patients (International Classification of Diseases (ICD)-10 diagnoses: F20.0, F25.0, F28.0, F29.0) (WHO, 1992), 166 were FES patients (ICD-10 diagnoses: F20.0) who formed our core analytic sample. Ethical permission was obtained from the South-London and Maudsley Mental Health NHS Foundation Trust (SLaM) and the Institute of Psychiatry Research Ethics Committee. All patients gave informed written consent after reading a detailed information sheet.

2.2. Tracing patients and data at follow-up

The detailed approach to follow-up is provided in Supplementary material and elsewhere (Ajnakina et al., 2017; Lally et al., 2016). As depicted in Fig. 1, we successfully followed-up 139 (83.7%) of the original FES cohort for a mean of 5 years after first presentation to psychiatric services and who had received adequate trials of antipsychotic medications during the follow-up period to ascertain their treatment resistant status. Because these data additionally included information on patients with first episode of schizophrenia spectrum disorder, we repeated the analyses on the extended cohort of 240 patients. Information at follow-up was collated from the electronic psychiatric records that are the primary clinical record-keeping system within the SLaM Trust (Stewart et al., 2009) using the WHO Life Chart Schedule (LCS) extended version (World Health Organization, 1994; Morgan et al., 2014; Susser et al., 2000). We used this measure at the end of the follow-up period to obtain standardised retrospective assessments of patients' experiences, clinical and social outcomes that were reported by treating clinicians for the entire period of illness. The illness period was operationalised as the period from first contact with mental health services to the date of the last assessment recorded in electronic notes. The LCS measure has been widely used in prospective and retrospective studies (Ajnakina et al., 2017; Schoeler et al., 2017).

Using the LCS extended version we collected detailed information on in-/out-patient medication history including the number of antipsychotic medications used prior to commencing clozapine, medication initiation/discontinuation dates, antipsychotic dose, and the reasons for changing or discontinuing each antipsychotic medication such as lack of therapeutic effects, intolerance of antipsychotic medications or self-discontinuation of each medication (Lally et al., 2016). We extracted detailed information on reasons for each re-admission throughout the entire follow-up period, and corresponding admission and discharge dates.

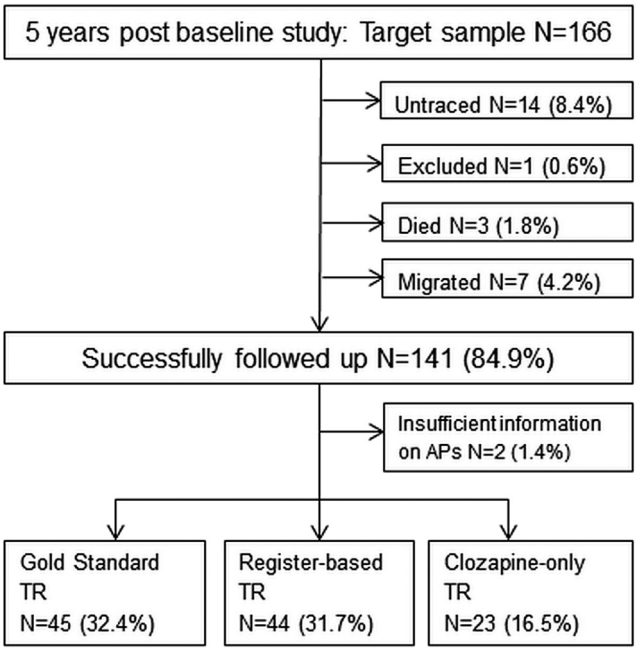

Fig. 1. Flow chart documenting how patients with first episode schizophrenia were traced five years after first contact with mental health services and administrative outcomes. APs, antipsychotic medications.

2.2.1. Gold standard definition of TRS

Following the National Institute for Health and Clinical Excellence (NICE) guideline (NICE guideline, 2014), patients were defined as having TRS if during the follow-up period they showed little or no symptomatic improvement to at least two consecutive treatments with antipsychotic medications of adequate dose and duration (≥6 weeks). A non-response to antipsychotic treatment was defined if 1) patients, having been treated with an antipsychotic medication of adequate dose and for an adequate duration did not show improvements in their clinical presentation as recorded by treating clinicians, and/or 2) the documented reason for switching antipsychotic medication was due to a lack of therapeutic response. An adequate dose of antipsychotic medication was defined according to a daily dose of ≥400 mg chlorpromazine equivalence (Leucht et al., 2014). We only included as TRS cases those patients who failed to respond and not those who were intolerant of antipsychotic medications or those who self-discontinued antipsychotic medication.

2.2.2. Algorithm-based definition of TRS

The algorithm-based definition of TRS was defined as treatment with clozapine in outpatient services and/or meeting the eligibility criterion for clozapine. The eligibility criterion entailed psychiatric hospital admission due to schizophrenia during antipsychotic treatment (as a proxy for insufficient treatment response) within 18 months after having had two outpatient consecutive periods of different treatments with antipsychotic medication for at ≥6 weeks' duration (Wimberley et al., 2016a, 2016b). We used outpatient lifetime clozapine prescription to define TRS.

2.3. Analyses

The predictive validity of the algorithm-based definition of TRS in determining treatment-resistant cases was evaluated with sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) (Parikh et al., 2008). All analyses were conducted in RStudio version 3.31 (Integrated Development for R. RStudio, Inc., Boston, MA).

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Table 1
Sensitivity, specificity, PPV, and NPV of the two algorithm-based definitions of treatment resistance schizophrenia (TRS) comparative to the gold standard definition of treatment resistance in patients with schizophrenia and schizophrenia spectrum disorders.

Definitions of TRS	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Schizophrenia (N = 139)				
Algorithm-based TRS (N = 44) vs gold standard (N = 45)	62.2	83.0	63.6	82.1
Clozapine (N = 23) vs gold standard (N = 45)	40.0	94.7	78.3	76.7
Schizophrenia spectrum disorders (N = 240)				
Algorithm-based TRS (N = 68) vs gold standard (N = 70)	60.0	84.7	61.7	83.7
Clozapine (N = 32) vs gold standard (N = 43)	38.6	97.1	84.4	79.3

TRS, treatment resistant schizophrenia; PPV, positive predictive value; NPV, negative predictive value.
Terminology: algorithm-based - TRS definition combined two criteria for TRS 1) outpatient clozapine prescription; 2) eligible criteria for clozapine; clozapine definition of TRS is solely based on outpatient clozapine prescription as the criterion for TRS.

3. Results

3.1. Core analytic cohort

The core analytic sample comprised 139 FES patients with a mean 5-year follow-up (SD = 2.5). Of these, 75.9% were male, 31.9% were of white ethnicity, and 46.1% were of black ethnicity. Of all patients, 45 (32.4%) met the gold standard definition of TRS. Applying the algorithm-based definition of TRS to the same cohort, 44 (31.7%) of patients were defined as TRS during the follow-up period. When applying the clozapine definition the proportion of TRS was 16.5% (N = 23/139) (Fig. 1).

3.2. Validation of the register-based definition of TRS

Sensitivity of the algorithm-based definition in determining TRS cases was 62.2%; specificity was 83.0%; PPV was moderate (63.6%), and NPV for this definition was high (82.1%) (Table 1). Sensitivity and PPV for the clozapine definition compared to the gold standard were 40.0% and 78.3%, respectively. These results remained largely unchanged when the sample was expanded to schizophrenia spectrum disorders (N = 240) (Table 1).

4. Discussion

Our results highlight that an algorithm-based definition of TRS, which includes both clozapine prescription and an eligibility criterion for clozapine, has a 64% chance of correctly identifying TRS cases. Sensitivity of this definition was moderate (62%) but higher than for the clozapine definition of TRS (40%). Because clozapine is under-prescribed in clinical practices (Howes et al., 2012), the clozapine definition inevitably omits some TRS patients leading to the reduced sensitivity. In comparison, the TRS definition that additionally includes the eligibility criterion for clozapine is broader in its scope, possibly capturing treatment resistant patients not taking clozapine. Still, a substantial proportion of TRS patients would not be detected using this algorithm-based definition of TRS. This may be explained by a number of reasons. In some cases re-admissions may be due to other reasons than insufficient treatment response, such as treatment non-adherence. Therefore, the sensitivity of this criterion for TRS may be improved by encompassing other functional or symptomatic criteria (Lally et al., 2017; Huber et al., 2008). Nonetheless, large population-based registers, including the Danish registries, tend to lack information on symptoms. Further, for such registers, data on medications is available from outpatient prescriptions only. Having access to medication histories during hospitalisation may improve the sensitivity and positive predictive values observed for the algorithm-based definition of TRS; though this is also likely to be due to differences in care between the UK and Denmark. Further, the gold standard definition of TRS was based on clinical records and not individual/personal assessments for determining TRS. Nonetheless, it has been shown that it is possible to reliably quantify illness course using clinical notes (Bebbington et al., 2006). Additionally, because we validated two measures including clozapine prescription as a criterion for TRS, the gold standard definition of TRS did not include clozapine prescription and might thus not have identified all with TRS. However, although clozapine may be indicated for other reasons than treatment resistance, such as suicidality, we believe that nearly all schizophrenia patients prescribed clozapine are TRS. Therefore, in the present study we might have underestimated the positive predictive values of the algorithm-based definitions of TRS.

4.1. Conclusion

The extended algorithm-based definition indicative of insufficient treatment response to first-line treatment with antipsychotic medications and the clozapine definition should be utilised in combination to increase the probability of correctly classifying all true TRS cases.

Conflict of interest

CG has received grants from LA-SER Analytica and Eli-Lilly, outside the submitted work. JHM has received research funding from Lundbeck. All other authors declare no competing interests. The funders had no involvement in any aspect of the study.

Contributors

CG, TW, JHM and HTH devised the algorithms for detecting TRS in Danish registers. OA was responsible for data management, did statistical analyses, and wrote the first draft of the manuscript. All authors contributed to drafting the manuscript contributed equally to discussion of the study design and results, revised the manuscript, and approved the final version.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.02.017.

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References

Ajnakina, O., Lally, J., Di Forti, M., Kolliakou, A., Gardner-Sood, P., Lopez-Morinigo, J., Dazzan, P., Pariante, C.M., Mondelli, V., MacCabe, J., David, A.S., Gaughran, F., Murray, R.M., Vassos, E., 2017. Patterns of illness and care over the 5 years following onset of psychosis in different ethnic groups; the GAP-5 study. Soc. Psychiatry Psychiatr. Epidemiol. 5 (017-1417).

Bebbington, P.E., Craig, T., Garety, P., Fowler, D., Dunn, G., Colbert, S., Fornells-Ambrojo, M., Kuipers, E., 2006. Remission and relapse in psychosis: operational definitions based on case-note data. Psychol. Med. 36 (11), 1551–1562.

Di Forti, M., Sallis, H., Allegri, F., Trotta, A., Ferraro, L., Stilo, S.A., Marconi, A., La Cascia, C., Reis Marques, T., Pariante, C., Dazzan, P., Mondelli, V., Paparelli, A., Kolliakou, A., Prata, D., Gaughran, F., David, A.S., Morgan, C., Stahl, D., Khondoker, M., MacCabe, J.H., Murray, R.M., 2014. Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users. Schizophr. Bull. 40, 1509–1517.

Elkis, H., Buckley, P.F., 2016. Treatment-resistant schizophrenia. Psychiatr. Clin. North Am. 39 (2), 239–265.

Horsdal, H.T., Wimberley, T., Benros, M.E., Gasse, C., 2017. C-reactive protein levels and treatment resistance in schizophrenia—a Danish population-based cohort study. Hum. Psychopharmacol. https://doi.org/10.1002/hup.2632.

Howes, O.D., Vergunst, F., Gee, S., McGuire, P., Kapur, S., Taylor, D., 2012. Adherence to treatment guidelines in clinical practice: study of antipsychotic treatment prior to clozapine initiation. Br. J. Psychiatry 201, 481–485.

Howes, O.D., McCutcheon, R., Agid, O., de Bartolomeis, A., van Beveren, N.J., Birnbaum, M.L., Bloomfield, M.A., Bressan, R.A., Buchanan, R.W., Carpenter, W.T., Castle, D.J., Citrome, L., Daskalakis, Z.J., Davidson, M., Drake, R.J., Dursun, S., Ebdrup, B.H., Elkis, H., Falkai, P., Fleischacker, W.W., Gadelha, A., Gaughran, F., Glenthøj, B.Y., Graff-Guerrero, A., Hallak, J.E., Honer, W.G., Kennedy, J., Kinon, B.J., Lawrie, S.M., Lee, J., Leweke, F.M., MacCabe, J.H., McNabb, C.B., Meltzer, H., Möller, H.J., Nakajima, S., Pantelis, C., Reis Marques, T., Remington, G., Rossell, S.L., Russell, B.R., Siu, C.O., Suzuki, T., Sommer, I.E., Taylor, D., Thomas, N., Üçok, A., Umbricht, D., Walters, J.T., Kane, J., Correll, C.U., 2016. Treatment-resistant schizophrenia: treatment response and resistance in psychosis (TRRIP). Working group consensus guidelines on diagnosis and terminology. Am. J. Psychiatry 174, 216–229 (appiajp201616050503).

Huber, C.G., Naber, D., Lambert, M., 2008. Incomplete remission and treatment resistance in first-episode psychosis: definition, prevalence and predictors. Expert. Opin. Pharmacother. 9, 2027–2038.

Kane, J., Honigfeld, G., Singer, J., Meltzer, H., 1988. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. Arch. Gen. Psychiatry 45, 789–796.

Kennedy, J.L., Altar, C.A., Taylor, D.L., Degtiar, I., Hornberger, J.C., 2014. The social and economic burden of treatment-resistant schizophrenia: a systematic literature review. Int. Clin. Psychopharmacol. 29, 63–76.

Lally, J., Ajnakina, O., Di Forti, M., Trotta, A., Demjaha, A., Kolliakou, A., Mondelli, V., Reis Marques, T., Pariante, C., Dazzan, P., Shergil, S.S., Howes, O.D., David, A.S., MacCabe, J.H., Gaughran, F., Murray, R.M., 2016. Two distinct patterns of treatment resistance: clinical predictors of treatment resistance in first-episode schizophrenia spectrum psychoses. Psychol. Med. 8, 1–10.

Lally, J., Ajnakina, O., Stubbs, B., Cullinane, M., Murphy, K.C., Gaughran, F., Murray, R.M., 2017. Remission and recovery from first-episode psychosis in adults: systematic review and meta-analysis of long-term outcome studies. Br. J. Psychiatry https://doi.org/10.1192/bjp.bp.117.201475.

Leucht, S., Samara, M., Heres, S., Patel, M.X., Woods, S.W., Davis, J.M., 2014. Dose equivalents for second-generation antipsychotics: the minimum effective dose method. Schizophr. Bull. 40, 314–326.

Manuel, J.I., Essock, S.M., Wu, Y., Pangilinan, M., Stroup, S., 2012. Factors associated with initiation on clozapine and on other antipsychotics among Medicaid enrollees. Psychiatr. Serv. 63, 1146–1149.

Morgan, C., Lappin, J., Heslin, M., Donoghue, K., Lomas, B., Reininghaus, U., Onyejiaka, A., Croudace, T., Jones, P.B., Murray, R.M., Fearon, P., Doody, G.A., Dazzan, P., 2014. Reappraising the long-term course and outcome of psychotic disorders: the AESOP-10 study. Psychol. Med. 44 (13), 2713–2726.

National Collaborating Centre for Mental Health, 2009. Schizophrenia: core interventions in the treatment and management of schizophrenia in primary and secondary care. National Clinical Guideline Number 82, Updated edition British Psychological Society, Leicester.

National Institute for Health and Clinical Excellence guideline, 2014. Psychosis and Schizophrenia in Adults: Treatment and Management (Clinical Guideline 178). Royal College of Psychiatrists, London.

Parikh, R., Mathai, A., Parikh, S., Chandra Sekhar, G., Thomas, R., 2008. Understanding and using sensitivity, specificity and predictive values. Indian J. Ophthalmol. 56 (1), 45–50.

Schoeler, T., Petros, N., Di Forti, M., Klamerus, E., Foglia, E., Murray, R., Bhattacharyya, S., 2017. Poor medication adherence and risk of relapse associated with continued cannabis use in patients with first-episode psychosis: a prospective analysis. Lancet Psychiatry 4 (8), 627–633.

Stewart, R., Soremekun, M., Perera, G., Broadbent, M., Callard, F., Denis, M., Hotopf, M., Thornicroft, G., Lovestone, S., 2009. The South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLAM BRC) case register: development and descriptive data. BMC Psychiatry 9, 9–51.

Susser, E., Finnerty, M., Mojtabai, R., Yale, S., Conover, S., Goetz, R., Amador, X., 2000. Reliability of the life chart schedule for assessment of the long-term course of schizophrenia. Schizophr. Res. 42 (1), 67–77.

Wheeler, A.J., Feetam, C.L., Harrison, J., 2014. Pathway to clozapine use: a comparison between a patient cohort from New Zealand and a cohort from the United Kingdom. Clin. Drug Investig. 34, 203–211.

Wimberley, T., Pedersen, C.B., MacCabe, J.H., Støvring, H., Astrup, A., Sørensen, H.J., Horsdal, H.T., Mortensen, P.B., Gasse, C., 2016a. Inverse association between urbanicity and treatment resistance in schizophrenia. Schizophr. Res. 174 (1–3), 150–155.

Wimberley, T., Stovring, H., Sorensen, H.J., Horsdal, H.T., MacCabe, J.H., Gasse, C., 2016b. Predictors of treatment resistance in patients with schizophrenia: a population-based cohort study. Lancet Psychiatry 3, 358–366.

Wimberley, T., Gasse, C., Meier, S.M., Agerbo, E., MacCabe, J.H., Horsdal, H.T., 2017a. Polygenic risk score for schizophrenia and treatment-resistant schizophrenia. Schizophr. Bull. 10 (10).

Wimberley, T., MacCabe, J.H., Laursen, T.M., Sørensen, H.J., Astrup, A., Horsdal, H.T., Gasse, C., Støvring, H., 2017b. Mortality and self-harm in association with clozapine in treatment-resistant schizophrenia. Am. J. Psychiatry 174 (10), 990–998.

World Health Organization, 1992. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. World Health Organization, Geneva, Switzerland.

World Health Organization, 1994. Schedules for Clinical Assessment in Neuropsychiatry: Version 2: Manual: World Health Organization, Division of Mental Health.

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